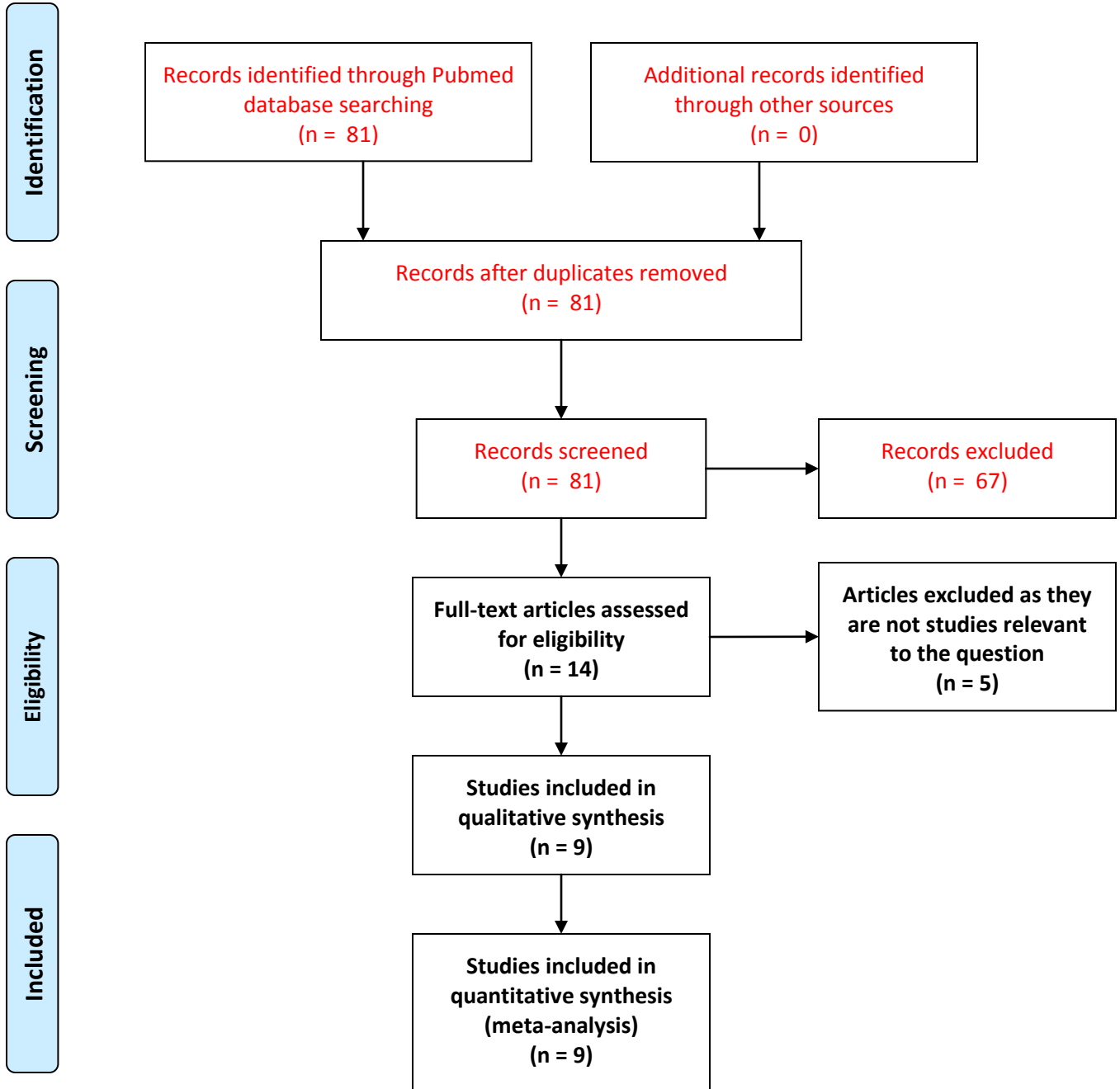




Republic of the Philippines  
Department of Health  
**OFFICE OF THE SECRETARY**

<b>Name of medicine (INN):</b>	<b>Esomeprazole tablet and injection</b>
<b>Indication:</b>	Treatment of Gastroesophageal Reflux Disease (GERD) Risk reduction of NSAID-associated gastric ulcer H. pylori eradication to reduce the risk of duodenal ulcer recurrence Long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison Syndrome.
<b>Date of deliberation:</b>	24 July 2015
<b>Recommendation:</b>	<b>DISAPPROVAL</b>
<b>Clinical evidence:</b>	<p>Esomeprazole was found to be more effective in H. pylori eradication than first generation PPI (32%) but with a wide confidence interval (95%CI: 27%-99%). On the other hand, it is equally effective compared to rabeprazole. In terms of safety, one meta-analysis (Sultan et al, 2008) showed that there was no significant difference in the increase in incidence of respiratory infection among esomeprazole and other PPIs. Likewise, same result was seen with regard to the increased incidence of cardiac events.</p> <p><i>(See Attachment for the full ERG evaluation)</i></p>
<b>Cost data:</b>	<p>It was noted that the total cost for a 7 day eradication treatment with esomeprazole 20 mg will be Php 503.16 compared to omeprazole at Php 347.48. The incremental cost per patient for the esomeprazole treatment was computed at Php 155.68.</p> <p><i>(See Attachment).</i></p>
<b>Remarks:</b>	The Secretary of Health has officially disapproved the proposal to include esomeprazole in the PNF. There was no appeal received within the set deadline, thus the recommendation of the Council still remains.

PRISMA Table



1) What is the comparative clinical effectiveness of proton pump inhibitors (PPIs) in H. pylori eradication and improving gastric healing rates among patients with gastric ulcer? 2) How are the different proton pump inhibitors compared in terms of safety (all AEs)? 3) What are the comparative treatment costs per patient of the different PPIs?

**EVIDENCE TABLE 1**

NO	TITLE/ AUTHOR YEAR/JOURNAL	STUDY DESIGN	PARTICIPANT DESCRIPTION	INTERVENTION	RESULTS/OUTCOMES					GRADE OF EVIDENCE	REMARKS
					EVENTS	Esomeprazole/ experimental		Control			
					(including adverse events)	No. of events *	Total # of patients	No. of events *	Total # of patients		
1	McNicholl et al. Aliment Pharmacol Ther, 2012	Meta-analysis	25 RCTs of 5,998 patients positive for H pylori	Esomeprazole vs. 1 <sup>st</sup> generation PPI	H pylori eradication	1,020	1,240	1,054	1,358		OR=1.32; 95%CI: 1.01 and 1.73
				Rabeprazole vs. esomeprazole	H pylori eradication	592	772	631	802		OR=0.90; 95%CI: 0.70 and 1.17
2	Gisbert et al. Digestive Liver Disease, 2004	Meta-analysis	5 RCTs on patients with peptic ulcer disease	Esomeprazole vs. omeprazole	H pylori eradication rate	Events not reported in text	648	Events not reported in text	644		RR=1.19; 95%CI: 0.81 and 1.74
3	Wang et al. Digestion, 2006	Meta-analysis	11 RCTs on 2,159 patients with H pylori	Esomeprazole vs. PPIs	H pylori eradication rate	Events not reported in text	1,117	Events not reported in text	1,029		RR=1.39; 95%CI: 1.09 and 1.75
4	Nishida et al. Wrold J Gastroenterol, 2014	RCT	268 patients with gastric or duodenal ulcer	Esomeprazole vs. lansoprazole	H pylori eradication rate	69.4%	134	73.9%	134		NS
					Total adverse event	75 (56%)	71 (53%)	NS			
5	Edwards et al. Alimentary Pharma Ther, 2006	Meta-analysis	8 RCTs on patients with reflux esophagitis	PPIs (omep, lanso, panto) vs. esomepraz	Healing rates (endoscopy week 8)	Events not reported in text	6,787	Events not reported in text	6,785		RR=0.95; 95%CI: 0.94 and 0.97
				Lansopraz vs. esomeprazole	Healing rates (endoscopy week 8)				RR=0.96; 95%CI: 0.94 and 0.98		

				Omeprazole vs. esomeprazole	Healing rates (endoscopy week 8)						RR=0.93; 95%CI: 0.91 and 0.95
				Pantopraz vs. esomeprazole	Healing rates (endoscopy week 8)						RR=0.98; 95%CI: 0.95 and 1.00
6	Edwards et al. Aliment Pharma Thera, 2001	Meta-analysis	12 RCTs on patients with reflux esophagitis	Esomeprazole vs. omeprazole	Healing rates (endoscopy week 8)	2,167	2,446	1,998	2,431		RR=1.08; 95%CI: 1.05 and 1.10
7	Gralnek et al. Clin Gastroenterol Hepatol, 2006	Meta-analysis	10 RCTs on 15,316 erosive esophagitis patients	Esomeprazole vs. other PPIs (omeprazole, lansoprazole, pantoprazole)	Erosive esophagitis (healing after 8 wks) GERD symptom relief	Events not reported in text		Events not reported in text			OR=1.10; 95%CI: 1.05 and 1.15 OR=1.08; 95%CI: 1.08 and 1.11
8	Sultan et al. Can J Gastroenterol, 2008	Meta-analysis	7 RCTs of 2,586 patients given PPI for various conditions	Esomeprazole vs. placebo Rabeprazole vs. placebo Pantoprazole vs. placebo Omeprazole vs. placebo	Respiratory infection	36 2 25 21	689 133 521 600	19 0 9 8	685 140 246 300		
9	Kwok et al. Int'l J Cardiol, 2012	Meta-analysis	23 RCTs on 222,311 patients prescribed with PPI	Esomeprazole vs. placebo Omeprazole vs. placebo Lansoprazole vs. placebo Pantoprazole vs. placebo	Major adverse cardiac events	Events not reported in text		Events not reported in text			OR=1.32; 95%CI: 1.09 and 1.60 OR=1.24; 95%CI: 1.07 and 1.43 OR=1.39; 95%CI: 1.23 and 1.57 OR=1.41; 95%CI: 1.21 and 1.64

				Rabeprazole vs. placebo								OR=1.38; 95%CI: 0.78 and 2.45
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**EVIDENCE TABLE 2: GRADE EVIDENCE PROFILE TABLE**

QUALITY ASSESSMENT							SUMMARY OF FINDINGS					Importance
No. of Studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No. of patients		Effect		Over-all Quality	
							Intervention	Control	Relative (95% CI)	Absolute MD		
Outcome: H pylori eradication												
1	Meta-analysis	None	None	None	None		Esomeprazole	1 <sup>st</sup> generation PPI	1.32; 95%CI: 1.01 and 1.73		High	Critical
Outcome: H pylori eradication												
1	Meta-analysis	None	None	None	None		Esomeprazole	Rabeprazole	0.90; 95%CI: 0.70 and 1.17		High	Critical

**DETAILS REQUIRED FOR COST-EFFECTIVENESS ANALYSIS**

<p><b>PARAMETER</b> (Indicate information for intended recipient)* <b><u>INTENDED RECIPIENT:</u></b></p>	<p><b>NEW MEDICINE OR PROPOSED NEW INDICATION/ FORMULATION/ ROUTE OF ADMINISTRATION</b></p>	<p><b>CURRENTLY LISTED MEDICINE FOR SAME INDICATION IN THE PNF</b></p>	<p><b>REFERENCES</b></p>
<p>COST PER DOSAGE UNIT (in PhP)                      a. Proposed list price to the government                      b. Current prevailing market price</p>	<p><sup>1</sup>Esomeprazole 40 mg P 21.50 per tab   <sup>2</sup>Clarithromycin 500 mg tablet (P 12.00 per tab)   <sup>2</sup>Amoxicillin 500 mg (P1.22 per cap)</p>	<p><sup>2</sup>Omeprazole 40 mg P 10.38 per cap   <sup>2</sup>Clarithromycin 500 mg tablet (P 12.00 per tab)   <sup>2</sup>Amoxicillin 500 mg (P1.22 per cap)</p>	<p><sup>1</sup> market price of generic esomeprazole   <sup>2</sup>DPRI</p>
<p>NUMBER OF DOSAGE UNITS PER UNIT COURSE</p>	<p>14                       Clarithro (14)                       Amox (28)</p>	<p>14                       Clarithro (14)                       Amox (28)</p>	
<p>TOTAL DIRECT COST PER PATIENT PER TREATMENT COURSE (in PhP)</p>	<p><b>Php 503.16</b></p>	<p><b>Php 347.48</b></p>	
<p>ADDITIONAL COST PER PATIENT PER TREATMENT COURSE: (n PhP)</p>			
<p>TOTAL COST PER PATIENT PER TREATMENT COURSE (in PhP) Total Direct + Additional Costs</p>	<p><b>Php 503.16</b></p>	<p><b>Php 347.48</b></p>	
<p>ESTIMATED NUMBER OF PATIENTS WITH THE DISEASE/CONDITION WHO WILL USE THE MEDICINE</p>			
<p>QUALITY ADJUSTED LIFE YEARS (IF AVAILABLE)</p>			
<p>DISABILITY ADJUSTED LIFE YEARS (IF AVAILABLE)</p>			

## REVIEWERS' RECOMMENDATIONS

### Literature Search

- We searched Pubmed database last April 17, 2015 using the terms “esomeprazole” and limit to meta-analysis. This yielded 23 articles. We reviewed the articles and the last meta-analysis was dated 2012. We updated the search to “esomeprazole” and limit to randomized controlled trials published from January 2012 to present. This yielded 58 articles. We reviewed all the 81 abstracts and considered 14 articles for full text retrieval.
- We reviewed the 14 articles and included 9 in this review. The included articles were:
  - McNicholl AG(1), Linares PM, Nyssen OP, Calvet X, Gisbert JP. Meta-analysis: esomeprazole or rabeprazole vs. first-generation pump inhibitors in the treatment of *Helicobacter pylori* infection. *Aliment Pharmacol Ther.* 2012 Sep;36(5):414-25. doi: 10.1111/j.1365-2036.2012.05211.x. Epub 2012 Jul 15.
  - Kwok CS(1), Jeevanantham V, Dawn B, Loke YK. No consistent evidence of differential cardiovascular risk amongst proton-pump inhibitors when used with clopidogrel: meta-analysis. *Int J Cardiol.* 2013 Aug 10;167(3):965-74. doi: 10.1016/j.ijcard.2012.03.085. Epub 2012 Mar 30.
  - Sultan N(1), Nazareno J, Gregor J. Association between proton pump inhibitors and respiratory infections: a systematic review and meta-analysis of clinical trials. *Can J Gastroenterol.* 2008 Sep;22(9):761-6.
  - Gralnek IM(1), Dulai GS, Fennerty MB, Spiegel BM. Esomeprazole versus other proton pump inhibitors in erosive esophagitis: a meta-analysis of randomized clinical trials. *Clin Gastroenterol Hepatol.* 2006 Dec;4(12):1452-8.
  - Edwards SJ(1), Lind T, Lundell L. Systematic review: proton pump inhibitors (PPIs) for the healing of reflux oesophagitis - a comparison of esomeprazole with other PPIs. *Aliment Pharmacol Ther.* 2006 Sep 1;24(5):743-50.
  - Gisbert JP(1), Pajares JM. Esomeprazole-based therapy in *Helicobacter pylori* eradication: a meta-analysis. *Dig Liver Dis.* 2004 Apr;36(4):253-9.
  - Edwards SJ(1), Lind T, Lundell L. Systematic review of proton pump inhibitors for the acute treatment of reflux oesophagitis. *Aliment Pharmacol Ther.* 2001 Nov;15(11):1729-36.
  - Nishida T(1), Tsujii M(1), Tanimura H(1), Tsutsui S(1), Tsuji S(1), Takeda A(1), Inoue A(1), Fukui H(1), Yoshio T(1), Kishida O(1), Ogawa H(1), Oshita M(1), Kobayashi I(1), Zushi S(1), Ichiba M(1), Uenoyama N(1), Yasunaga Y(1), Ishihara R(1), Yura M(1), Komori M(1), Egawa S(1), Iijima H(1), Takehara T(1). Comparative study of esomeprazole and lansoprazole in triple therapy for eradication of *Helicobacter pylori* in Japan. *World J Gastroenterol.* 2014 Apr 21;20(15):4362-9. doi: 10.3748/wjg.v20.i15.4362.

### Results of the Review

#### Effectiveness/Efficacy

- In a latest meta-analysis of 25 RCTs among 5,998 patients with peptic ulcer disease and positive for *H pylori*, esomeprazole was found to be better than first generation PPI by relative efficacy increase of 32% in terms of eradication and this was statistically significant (OR=1.32; 95%CI: 1.01 and 1.73). This finding was confirmed in two meta-analysis, McNicholl et al, 2012 and Wang et al, 2006. These two meta-analysis pooled results of 25 and 11 RCTs involving 5,998 and 2,159 patients respectively.
- In another meta-analysis however with smaller number of RCTs included, the eradication rate was not statistically significant between esomeprazole and omeprazole (RR=1.19; 95%CI: 0.81 and 1.74), Gisbert et al, 2004. In another smaller number of subjects i.e. RCT of 268 patients, esomeprazole did not significantly differ from lansoprazole (Nishida et al, 2014).
- When compared to rabeprazole, there was similar eradication rate (OR=0.90; 95%CI: 0.70 and 1.17).

- Among patients with GERD, 2 meta-analyses showed esomeprazole to be better than first generation PPI by about 10%, Gralnek et al, 2006 and Edwards et al, 2001.

### Safety

- In terms of safety, one meta-analysis (Sultan et al, 2008) showed that there was no significant difference in the increase in incidence of respiratory infection among esomeprazole and other PPIs when placebo-controlled studies were indirectly compared. A similar finding among PPIs was noted with the increase in incidence of major cardiac events when placebo-controlled studies were indirectly compared as well (Kwok et al, 2012). Although, there were no direct comparisons between the PPIs based on the reported odds ratio in the above meta-analysis in comparison of the different PPIs with placebo, the least cardiac events were noted with omeprazole (OR=1.24) followed by esomeprazole (OR=1.32)

### Summary of Review

- Overall, we found esomeprazole to be more effective than first generation PPI (32%) but with a wide confidence interval. It is also equally effective compared with rabeprazole. Its effect in increasing the incidence of respiratory infection and cardiac events is similar to other PPIs.

### Cost Data

- The total cost for a 7 day eradication treatment with Esomeprazole 20 mg as the PPI will be Php 503.16 compared with Omeprazole at Php 347.48. The incremental cost per patient for the esomeprazole treatment was computed at Php 155.68.

### Overall Recommendation

- Esomeprazole is more effective than 1<sup>st</sup> generation PPI by 32% but with wide confidence interval. However it also increased major cardiac events by the same rate. In addition, it is more expensive than omeprazole. Thus, there is not enough evidence or justification to include in the formulary.

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